Exercise and skeletal muscle carbohydrate metabolism during exercise: from MilkyWay™ to MEF2

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Muscle glycogen and blood glucose, derived from the liver glycogenolysis and gluconeogenesis and the gut following glucose ingestion, are key substrates for contracting skeletal muscle during prolonged, strenuous exercise. Fatigue during such exercise is often associated with muscle glycogen depletion and hypoglycemia.

My journey in exercise physiology began as an undergraduate through my involvement in a small project on maximal oxygen uptake in elite rowers with Dr. Mary Chennells at The University of Melbourne in 1981. However, it was really consolidated during my Masters degree with Prof. David Costill in the US, 1982-1984. At that time, his laboratory was actively involved in many projects on the applied physiology of endurance exercise and the potential of various nutritional interventions to enhance performance. My first project involved feeding chocolate bars (MilkyWay™) to cyclists during 4 h of intermittent cycling exercise. We observed that such feeding maintained blood glucose levels and rates of carbohydrate oxidation and resulted in a small, but significant, reduction in net muscle glycogen utilization (Hargreaves *et al.*, 1984). This alteration in glycogen metabolism was probably related to our exercise protocol, comprising periods of rest between low and high intensity exercise bouts, since subsequent studies utilizing continuous exercise at ~70% of maximum failed to observe any change in muscle glycogen use. One such study was the first of my doctoral work and formed the basis of my first presentation to this Society (Hargreaves & Briggs, 1986). Next, we focused on the regulation of glucose kinetics during exercise, including a study on the effect of carbohydrate ingestion on muscle glucose uptake and liver glucose production during prolonged, strenuous exercise (McConell *et al.*, 1994). We then turned our attention to the role of the facilitative glucose transporter GLUT4, which had been identified and cloned in the late 1980s, in increasing muscle glucose uptake during exercise. GLUT4 expression was higher in trained athletes compared with untrained subjects and was associated with enhanced insulin action and greater muscle glycogen storage (McCoy *et al.*, 1994). Translocation of GLUT4 to the sarcolemma is fundamental for muscle glucose uptake during exercise and was demonstrated in human skeletal muscle (Kristiansen *et al.*, 1996).

Over the last decade, following our observation that a single exercise bout increased GLUT4 gene expression (Kraniou *et al.*, 2000), we have focused on the molecular regulation of GLUT4 expression in response to exercise. Our studies, have confirmed key roles for the transcription factor myocyte enhancer factor 2 (MEF2) and the transcriptional repressor histone deacetylase 5 (HDAC5; McGee & Hargreaves, 2006), and we have identified AMP-activated protein kinase as an important HDAC5 kinase that mediates effects on GLUT4 expression (McGee *et al.*, 2008). These latter studies provide just one example of how the tools of molecular biology can be deployed to better understand the integrated, physiological responses to exercise in health and disease.

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